Armed Forces College of Medicine

AFCM

Lecture Title

Purine metabolism

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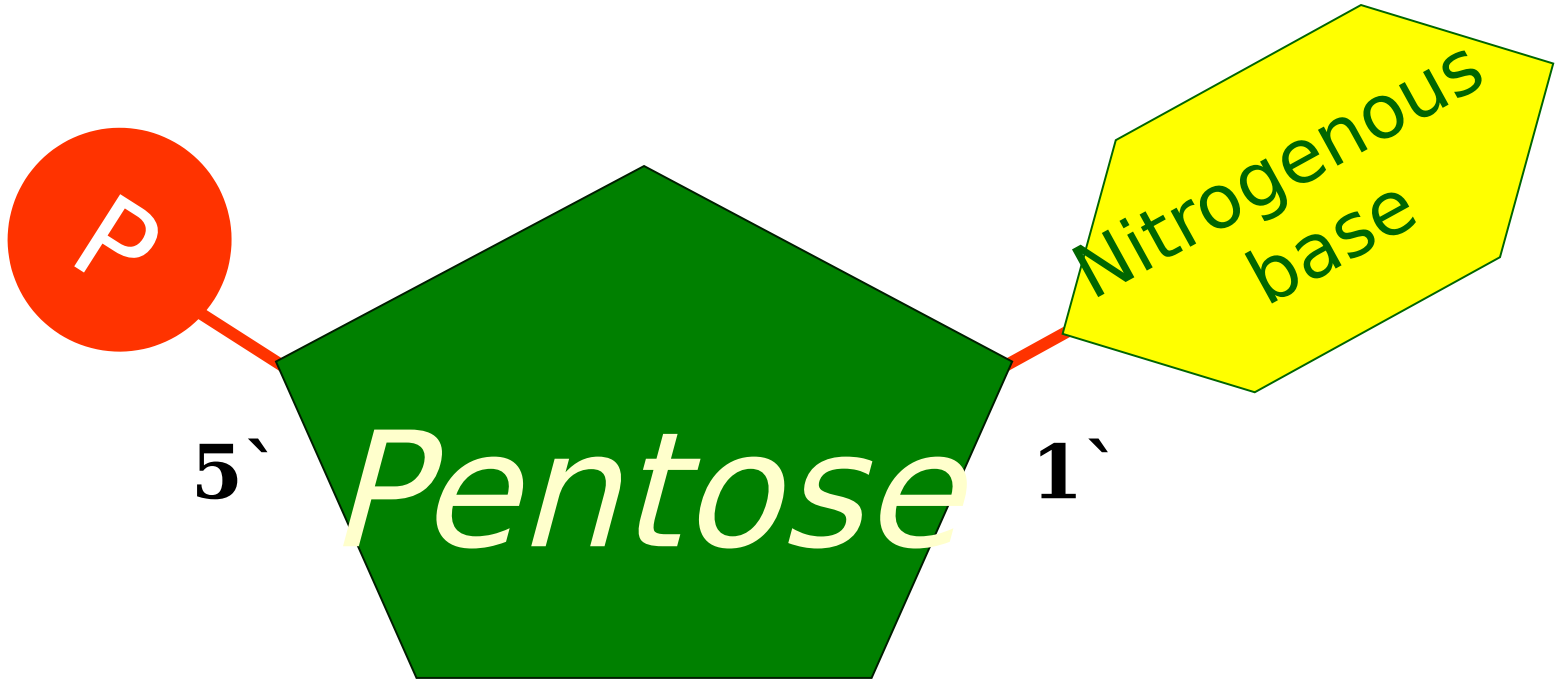
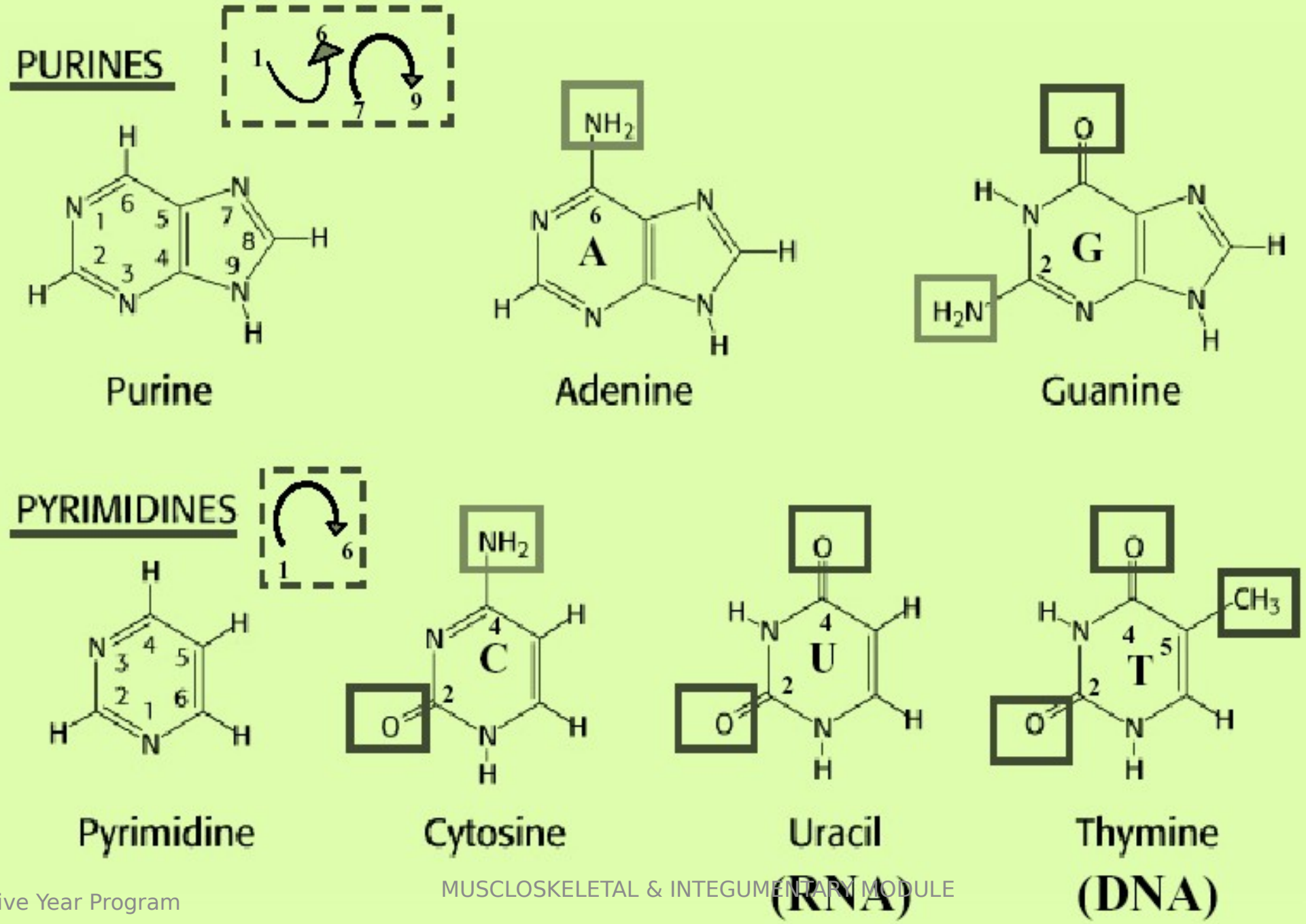
INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture the student will be able to:

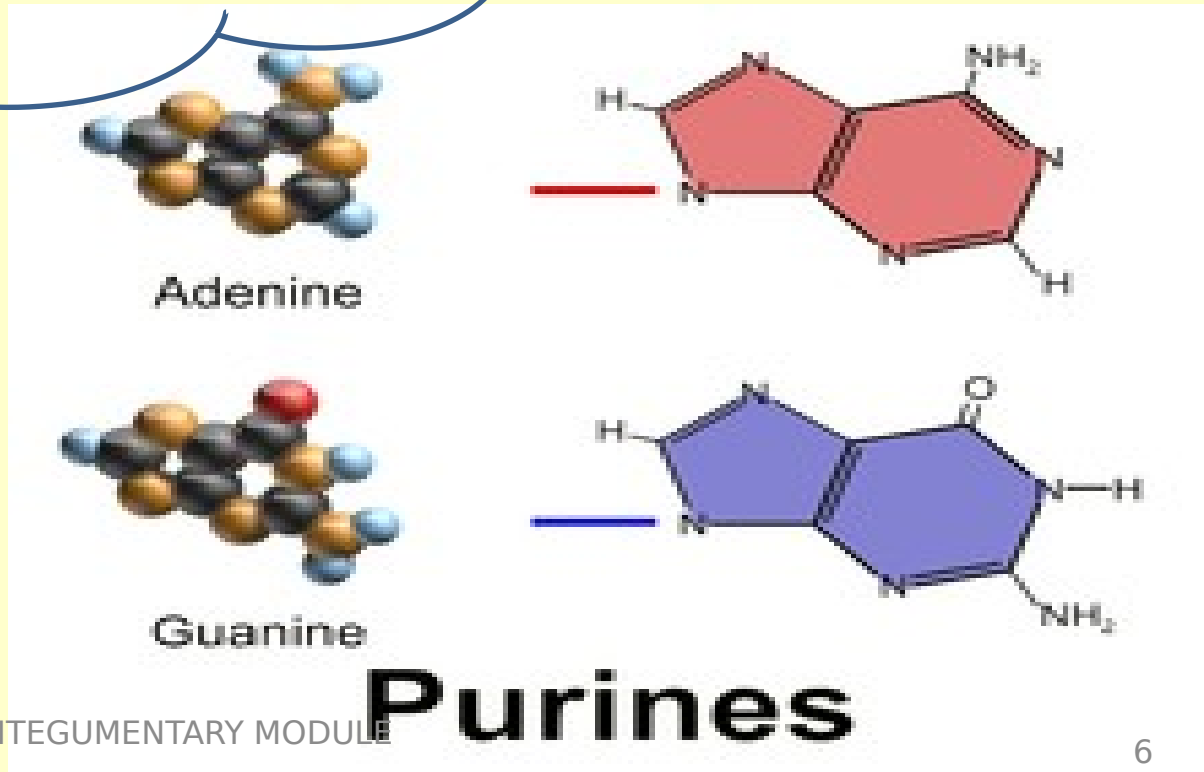
1. Illustrate steps of purine synthesis
2. Demonstrate regulation of purine metabolism
3. Explain biochemical basis of purine metabolism related-drugs

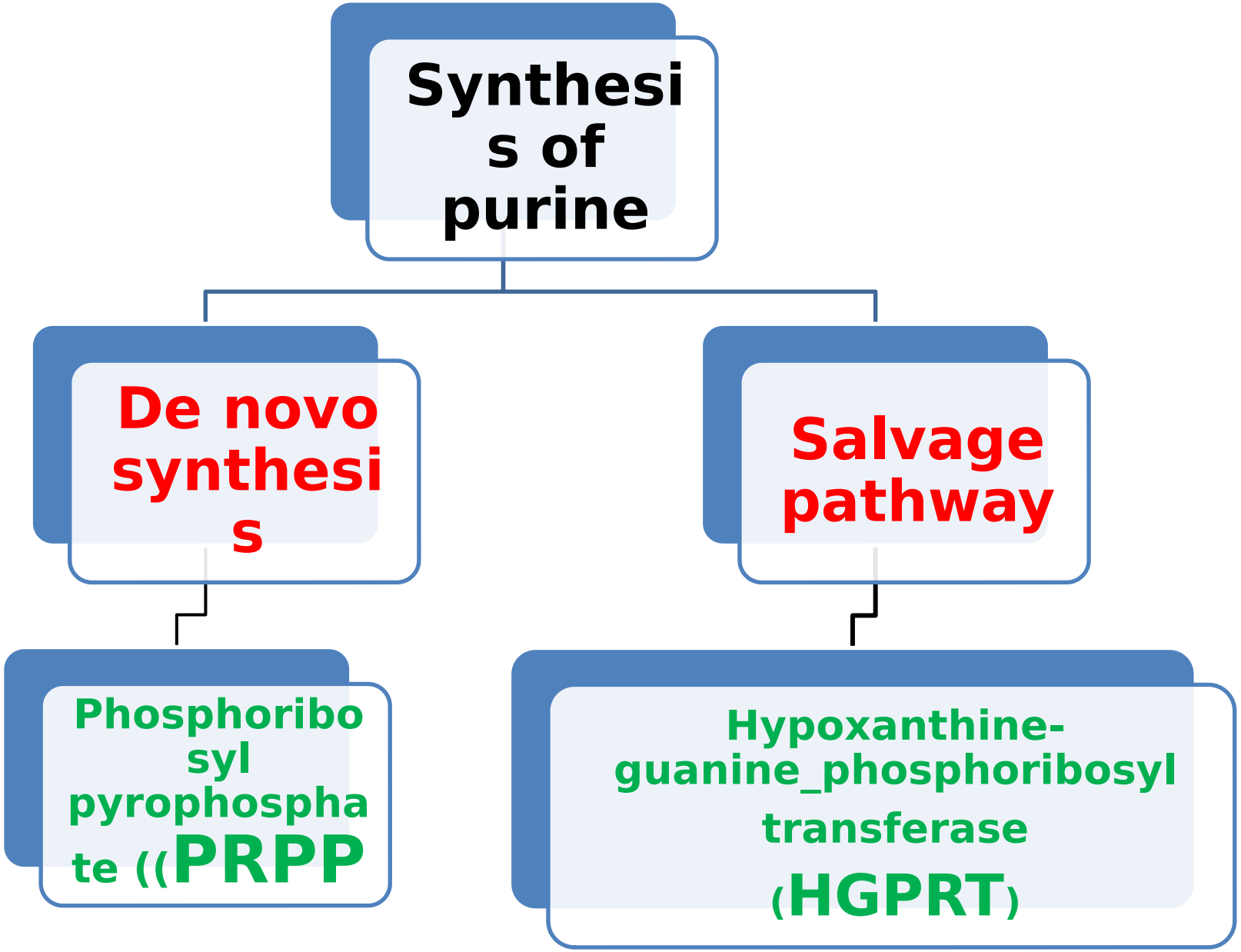
….Nucleotide….




PURINES
Purine
Adenine
Guanine
PYRIMIDINES
Pyrimidine
Cytosine
Uracil
Thymine
(RNA)
(DNA)

Purine synthesis



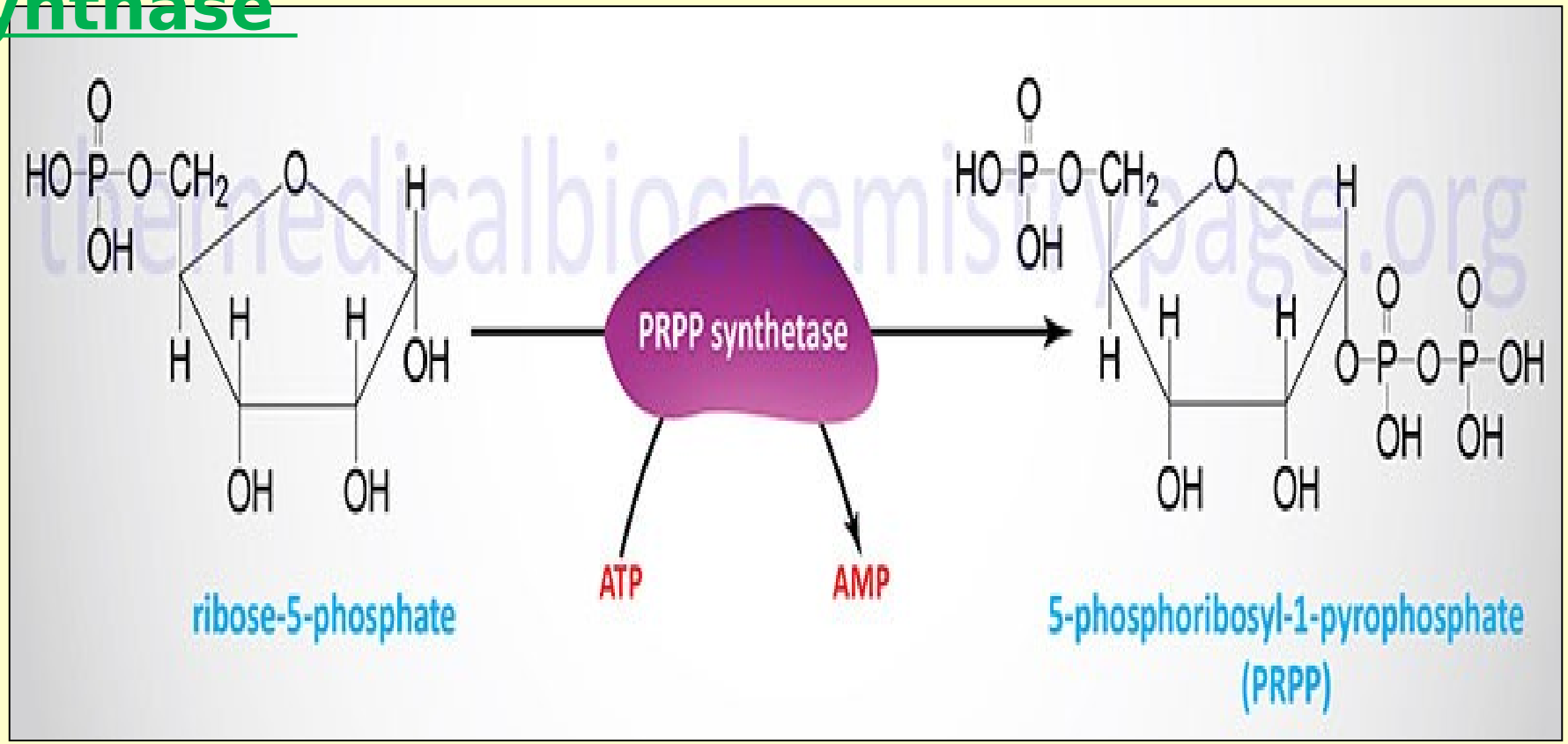

Synthesis of purine
De novo synthesis
Salvage pathway
Phosphoribosyl pyrophosphate ((PRPP
Hypoxanthine-guanine_phosphoribosyl transferase (HGPRT)

1- De Novo synthesis

- **All the enzymes of this pathway are present in *cytoplasm* of all cells**
- **Very active in the *liver* and *placenta***
- **The purine ring is constructed by adding carbon and nitrogen atoms step by step on a base of ribose-5-phosphate**
- **Purines are *NOT* made as free bases, but as *Nucleotides* in their phosphorylated forms**

1- First step

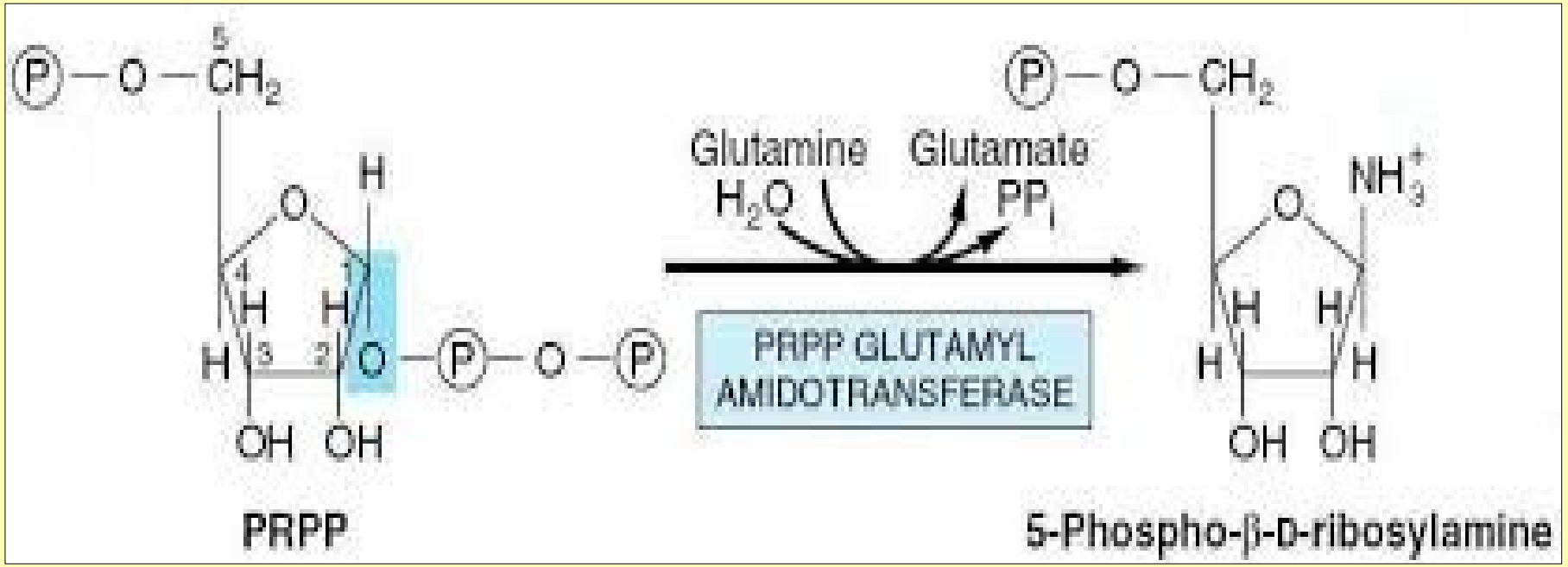
It is done by : phosphoribosyl-pyrophosphate synthase



Lippincott's Illustrated Reviews- 6th edition

2-Second Step

It is done by : Glutamine PRPP amidotransferase



It is the rate limiting step

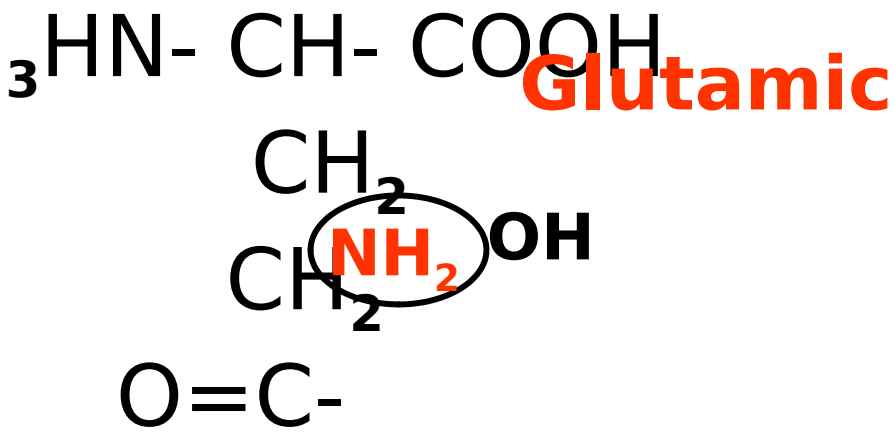
https://images.app.goo.gl/q9sHMBAGF9Kjv6gq5

2-Second Step

By Glutamine
PRPP
amidotransferase
(rate limiting enzyme)

5-Phosphoribosylamine

Glutamine+H2O



PRPP

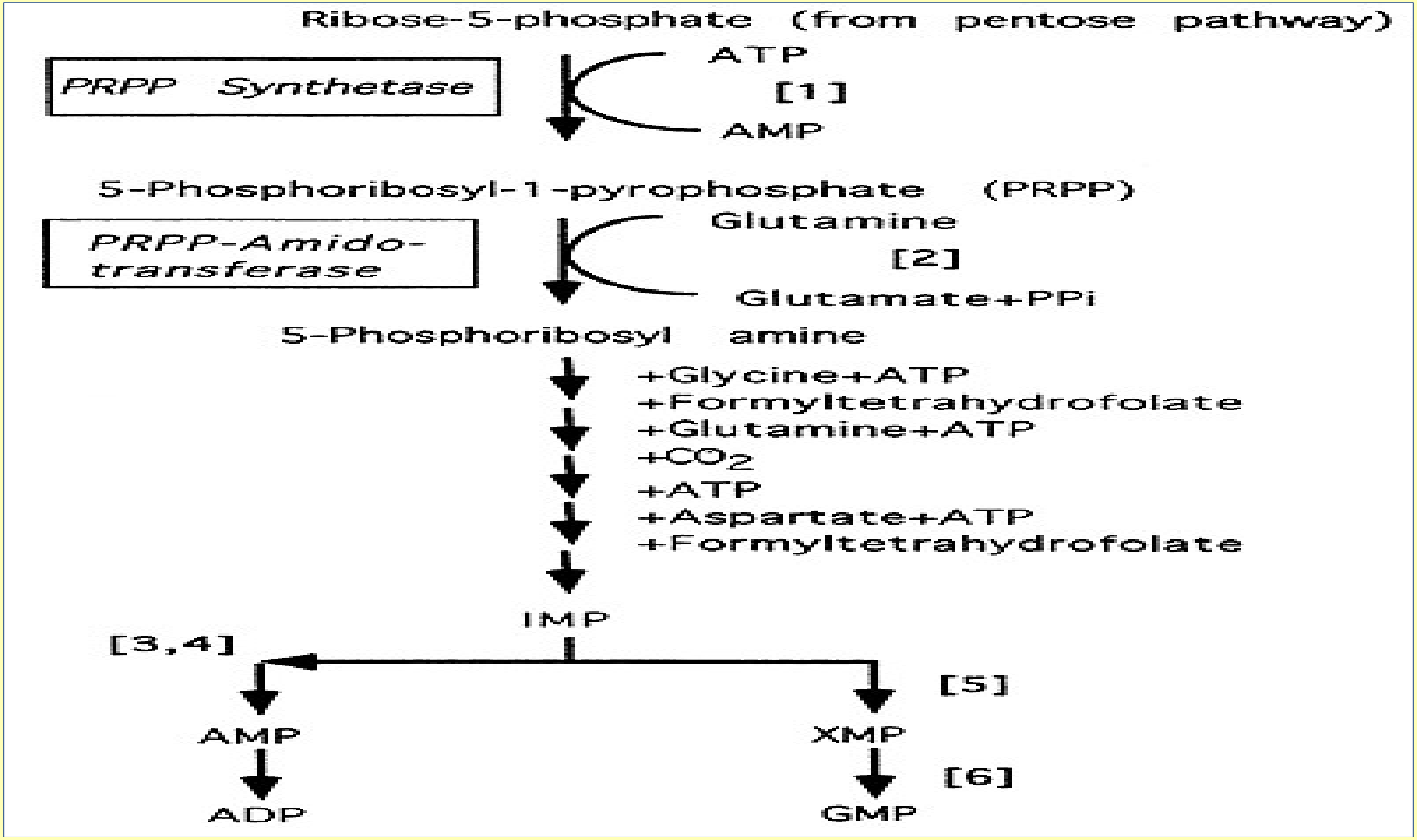
Purine synthesis:

1- Synthesis of PRPP from ATP and ribose 5-phosphate is catalyzed by PRPP synthetase **(**This enzyme is activated by *inorganic phosphate* and inhibited by *purine nucleotides*)

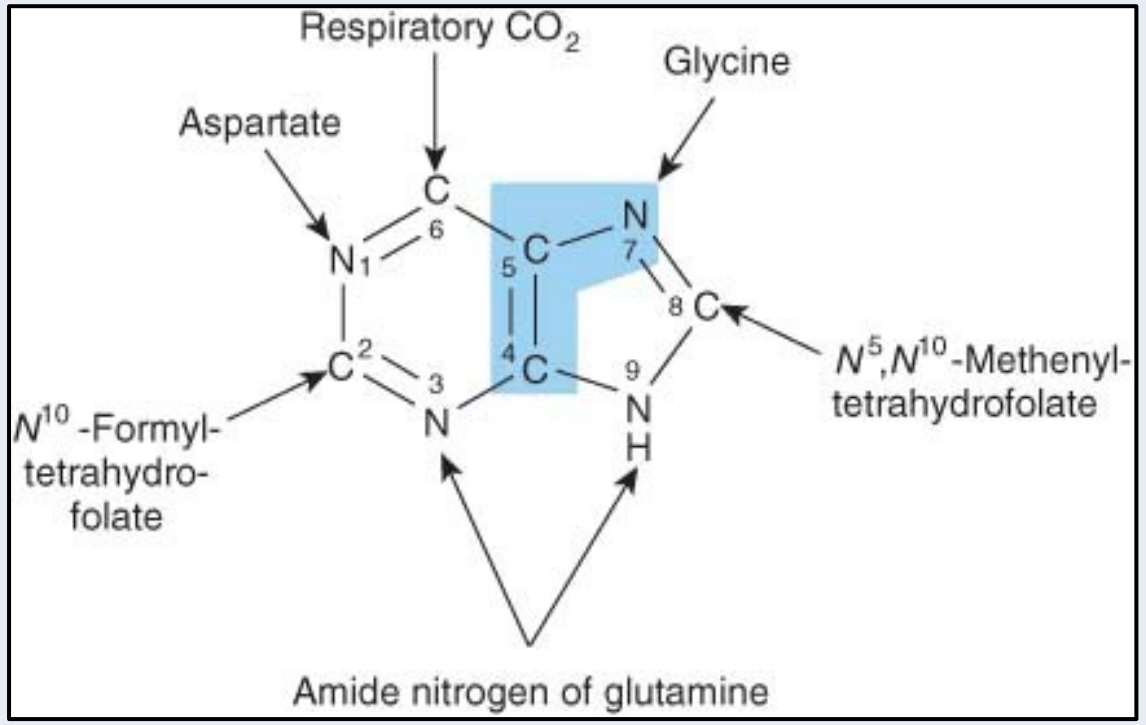
2. Synthesis of 5'-phosphoribosylamine from PRPP and glutamine. The amide group of glutamine replaces the

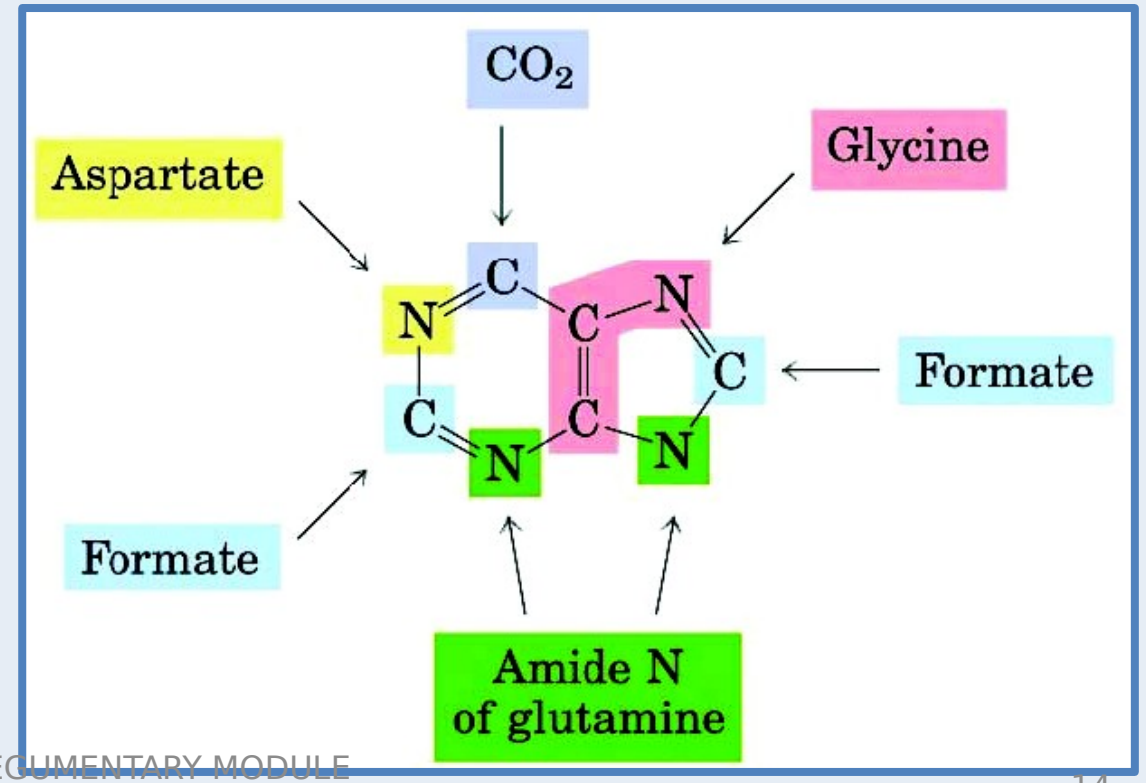
   pyrophosphate group attached to carbon 1 of PRPP (*This is the committed step in purine nucleotide biosynthesis)*

3- Other steps



Sources of carbon and nitrogen atoms in purine rings

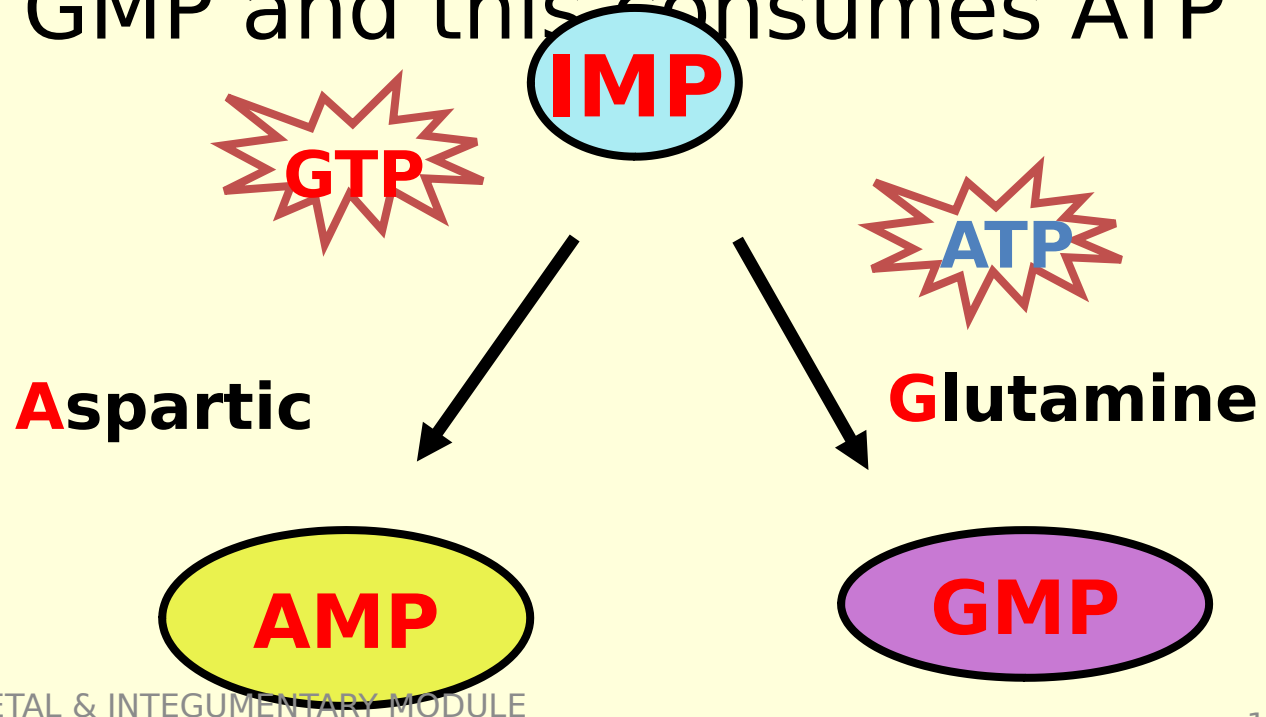




https://accessmedicine.mhmedical.com/Content.aspx?bookId=2386&sectionId=187833691

- The first nucleotide synthesized is **IMP** (inosine monophosphate) ..this requires 6 ATP.
- Then:

1. IMP is converted to AMP and this consumes GTP
   OR
2. IMP is converted to GMP and this consumes ATP



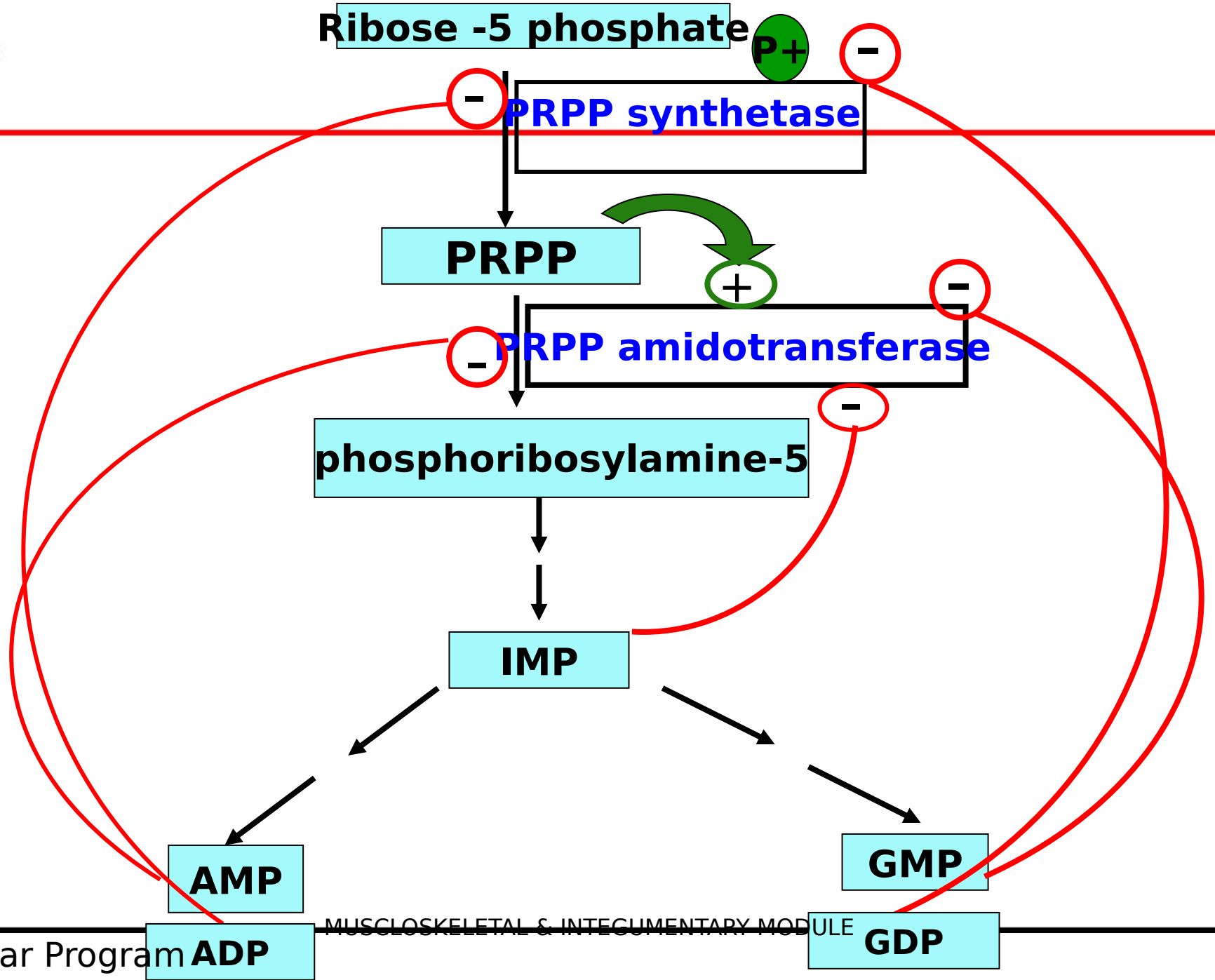
Regulation of de novo synthesis

1- **PRPP synthetase is allosterically inhibited by GMP,GDP and AMP,ADP.**

2. Glutamine PRPP amidotranseferase (*the committed step) is* allosterically inhibited by IMP,GMP, AMP and allosterically activated by PRPP.

3. Reciprocal control:

GTP is involved in AMP synthesis and ATP is involved in GMP synthesis


Ribose -5 phosphate
P+
PRPP synthetase
PRPP
PRPP amidotransferase
phosphoribosylamine-5
IMP
AMP
ADP
GMP
GDP

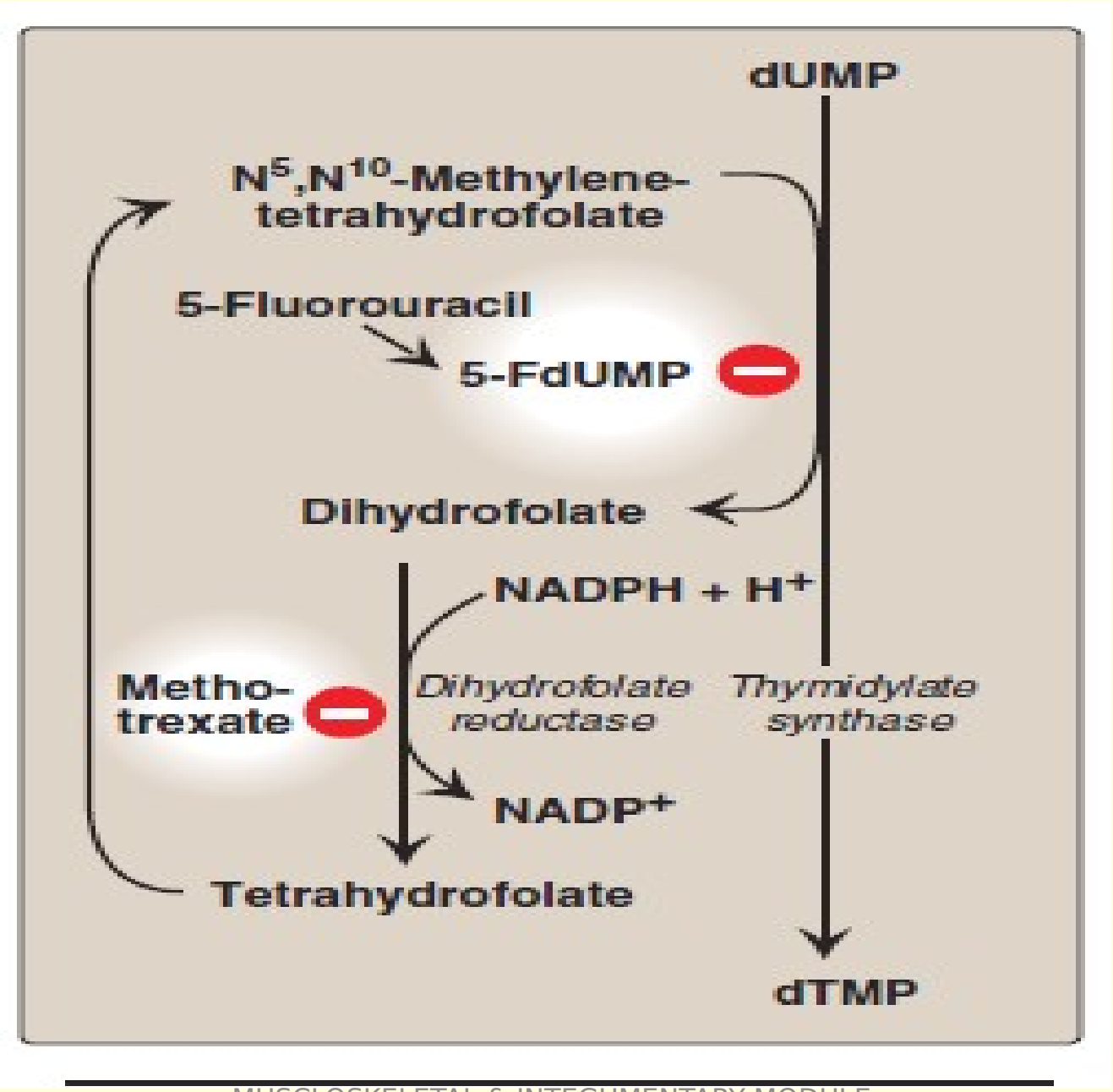
Medical Applications:

A) **Sulfonamides antibiotics inhibit bacterial synthesis of folic acid** ***(folic acid is needed for purine synthesis in bacteria).***

B) **Methotrexate is structural analog of folic acid is used as anticancer drugs as it i**

dihydrofolate reductase

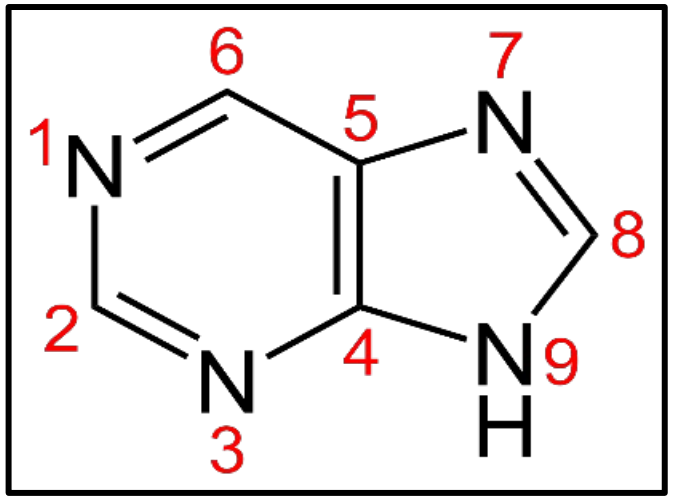
c) **6- mercaptopurine is structurally similar to IMP, so used as anticancer** ***(competitive inhibitor for conversion of IMP to either AMP or GMP)***



Lippincott's Illustrated Reviews- 6th edition

Lecture Quiz

- **What is the source of C4, 5 and N7 in this structure?**
- A. Glycine
- B. Aspartate
- C. Glutamine
- D. CO2
- E. Tetrahydrofolate

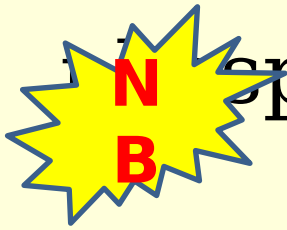


2- Salvage pathway

- Purines that result from:

1. Normal turnover of cellular nucleic acids
2. Nucleic acids of diet

are reused & converted to nucleotide



1.Up to 90% of Purines can be salvaged

2.It saves energy

3. It is a major pathway in most cells

Two enzymes only are needed:

Adenine phosphoribosyl transeferase (*APRT*)

Hypoxanthine – Guanine Phosphoribosyl transferase (*HGPRT*)

Salvage Pathway of Purine

✓ Two **phosphoribosyl transferases** are involved in this pathway:

- Adenosine phosphoribosyl transferase **(APRT)**

Adenine + PRPP ⟶ AMP + Ppi

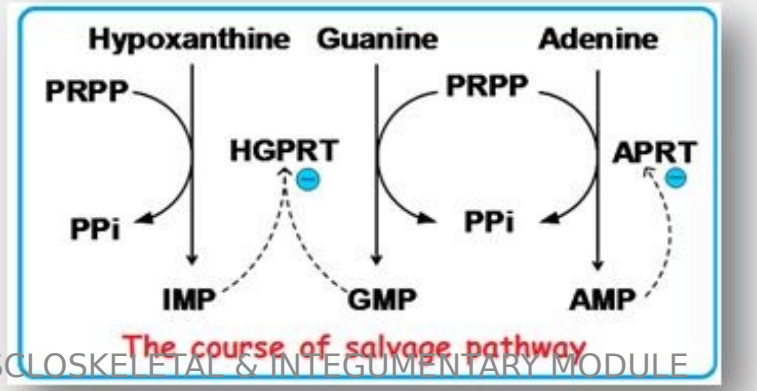
APRT is not very important because it generate little adenine

- Hypoxanthine-guanine phosphoribosyl transferase **(HGPRT)**

Hypoxanthine + PRPP ⟶ IMP + Ppi

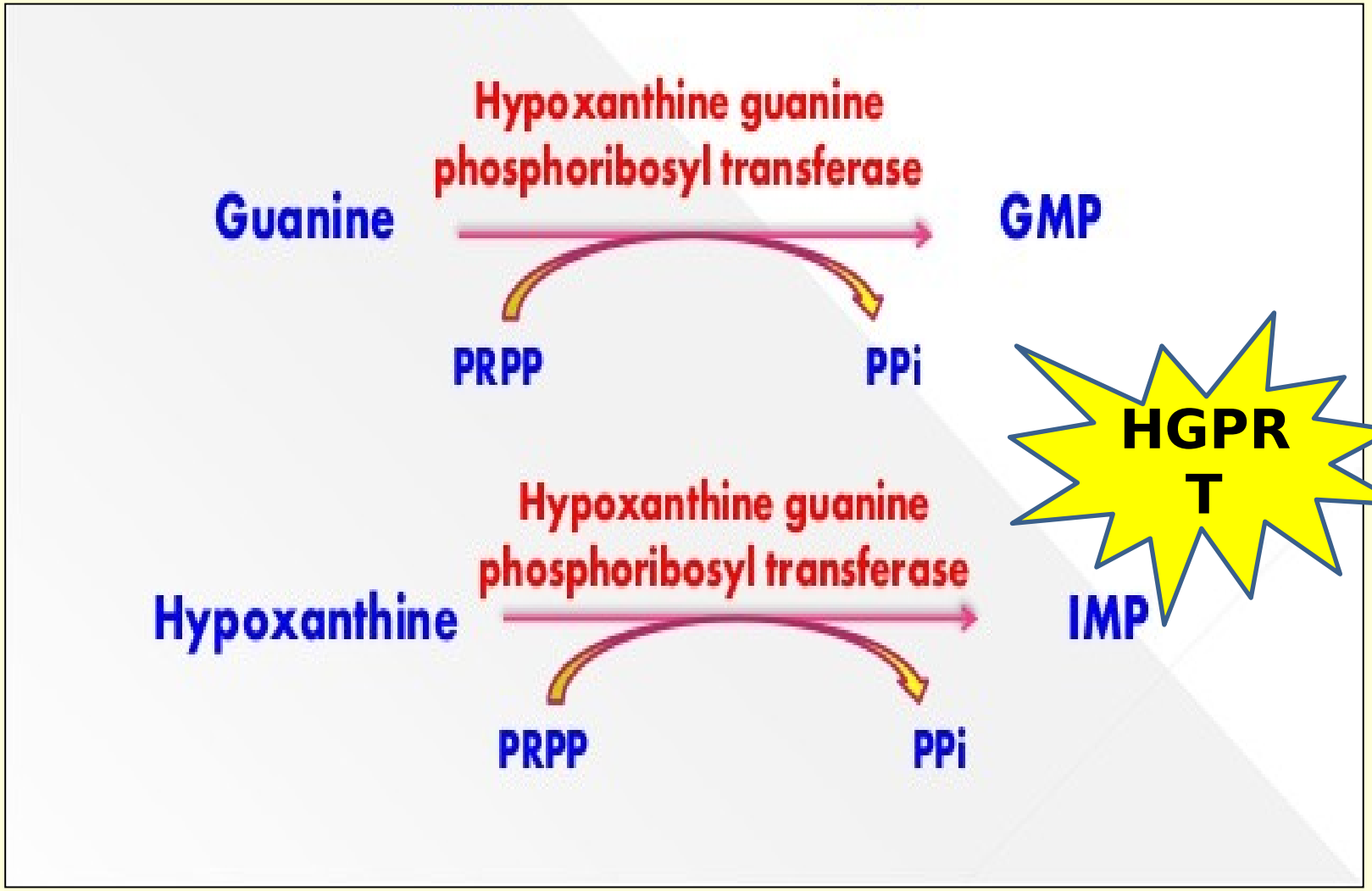
Guanine + PRPP ⟶ GMP + Ppi

HGPRT, is exceptionally important and it is inhibited by both IMP and GMP



The course of salvage pathway

2- Salvage pathway



https://slideplayer.com/slide/8003219/

Synthesis of Deoxyribonucleotides

- ***The nucleotides that are synthesized by both De Novo & Salvage Pathways are Ribonucleotides ……. for RNA***

- **DNA needs deoxyribonucleotides**

- ***It is done by Ribonucleotide reductase enzyme which needs 2 coenzymes;***

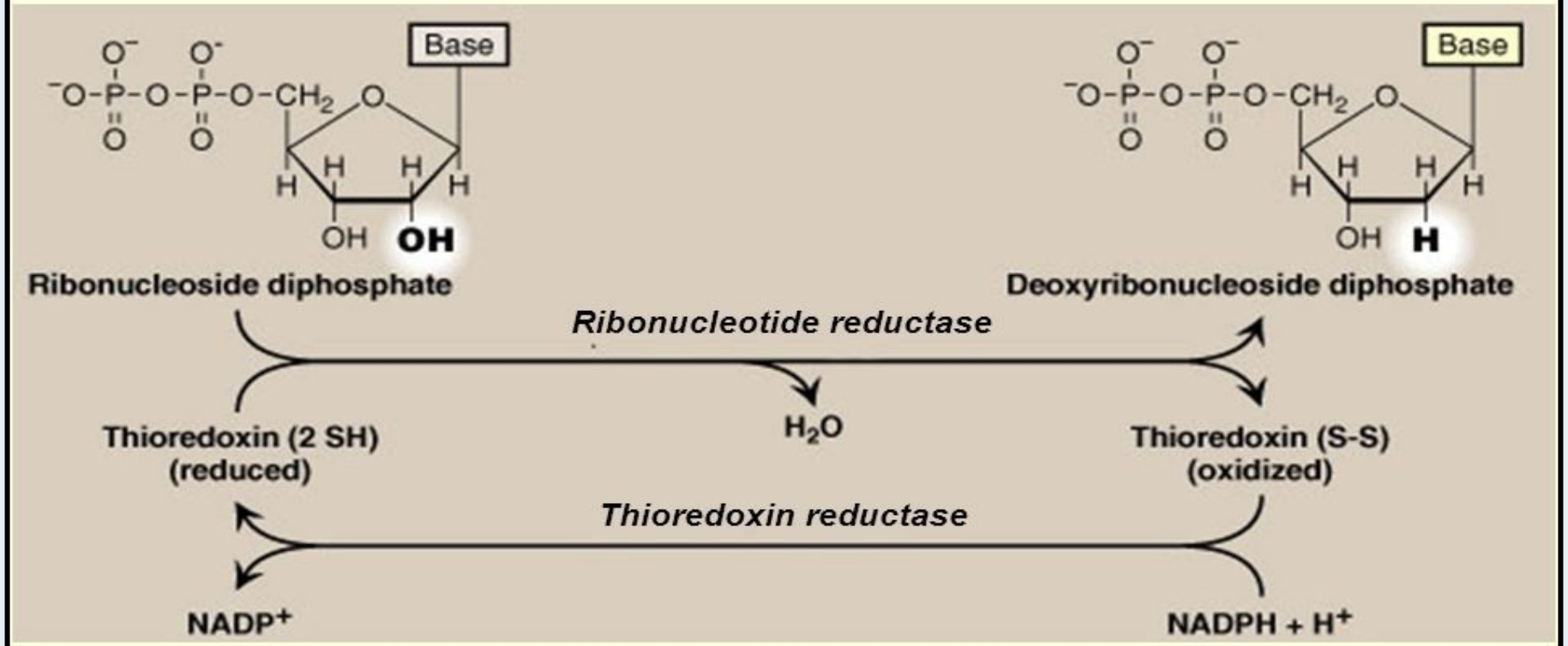
1-Thioredoxin

2- NADPH+H to regenerate the reduced Thioredoxin

- The enzyme is regenerated by **reduced thioredoxin** which donate their hydrogen atoms to ribonucleotide reductase forming **oxidized thioredoxin.**

- Regeneration of reduced thioredoxin is catalyzed by thioredoxin reductase and NADPH+H

Ribonucleotides to Deoxyribonucleotides



Inhibited by **dATP**; Activated by **ATP**

http://usmle.biochemistryformedics.com/hydroxyurea-in-the-treatment-of-leukemia/

Ribonucleotide reductase enzyme:

- **It reduces C_2 of ribose to be deoxyribose**

- **It is responsible for maintaining a balanced supply of deoxyribonucleotides for DNA synthesis**

- **Hydroxyurea:**

  Used in treatment of leukemia , because it inhibits ribonucleotide reductase enzyme so, inhibit DNA synthesis.

Lecture Quiz

- Hydroxyurea can be used in treatment of leukemia because it can inhibit:

1-Dihydrofolate reductase
2-Xanthine oxidase
3-Ribonucleotide reductase
4-IMP dehydrogenase

SUGGESTED TEXTBOOKS

- **<u>References:</u>**

- Lippincott’s Illustrated Reviews- 6th edition.
- Harper’s Illustrated Biochemistry-29th edition.

Dr. Maggie